EXHIBIT C

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL No. 2327**
THIS DOCUMENT RELATES TO WAVE 1 CASES	**JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

EXPERT REPORT OF JUAN C. FELIX, M.D.

I. Background and Qualifications

My name is Juan C. Felix, M. D. I am a physician licensed to practice medicine in the States of California, New York, New Jersey, Tennessee, Arizona, and Texas. I am board-certified in Anatomic Pathology with added qualification in Cytopathology. I received my medical degree from Cornell University Medical College in 1984. I completed a residency in Anatomic Pathology at the New York Hospital - Cornell University Medical College in 1988 and subsequently completed a fellowship in Obstetrical and Gynecological pathology at the same facility in 1989. I was appointed Assistant Professor of Pathology at Cornell University Medical College in 1989 where I practiced for two years and began my research career. I then moved to Southern California where I became an Assistant Professor of Pathology and Obstetrics and Gynecology at the University of Southern California (later to become the Keck School of Medicine of USC). In 1996, I was appointed Director of Obstetrical and Gynecological Pathology and Chief of Surgical Pathology at the Los Angeles County-University of Southern California Women's Hospital, one of the largest women's hospitals in the United States.

While at the Keck School of Medicine, I have been promoted to Associate Professor and later to Professor of Pathology and Obstetrics and Gynecology. I am currently a Professor of Clinical Pathology and Obstetrics and Gynecology at Keck School of Medicine of the University of Southern California, where I have served as Chief of Anatomic Pathology, Chief of Cytopathology and Director of Outreach Pathology.

My clinical and academic activities during most of my career have consisted almost exclusively of activities in Gynecological and Obstetrical Pathology, where I have

published over 110 peer-reviewed publications and authored eight textbook chapters. I am an expert consultant in the field of Gynecological and Obstetrical Pathology, where I render second opinions on difficult diagnostic cases from over 30 states and over 10 different countries, including in Europe, Asia, and North and South America. I have given invited lectures on gynecological pathology in many countries such as Taiwan, Spain, Portugal, Australia, Argentina, Brazil, Peru, Chile, Colombia, Panama, Costa Rica, Honduras, El Salvador, Mexico, and Canada.

For the last 17 years, I have served as an expert reviewer for leading scientific and medical journals in the field of gynecology and pathology; these include the American Journal of Surgical Pathology, American Journal of Pathology, Cytopathology, Acta Cytologica, Journal of Applied Immunohistochemistry and Molecular Morphology, Obstetrics and Gynecology, American Journal of Obstetrics and Gynecology, Gynecologic Oncology, Journal of the Lower Genital Tract, and Contraception, and have served on the editorial boards of Contraception and Journal of Applied Immunohistochemistry and Molecular Morphology. For a more detailed description of my education, training, and professional background please see my Curriculum Vitae, attached as exhibit A.

As a pathologist at one of the world's busiest gynecological hospitals that pioneers technologies in women's healthcare, I have had the opportunity to directly examine pelvic mesh explants from over fifty patients and evaluate the gross and histological characteristics of the tissue reaction associated with them. This experience predated my being approached to discuss my experience in the context of litigation. Although the majority of the samples were mesh explants from mid-urethral slings that were made out of Prolene, some of the samples were mesh explants associated with the repair of pelvic organ

prolapse that were made of other materials. In addition, as a consultant to pathologists and gynecologists both throughout the United States and from other countries, I have had many other mesh samples of various types sent to me for my expert opinion.

A list of materials that I have reviewed is attached as Exhibit B. All of the opinions expressed in this report are based upon my education, training, experience and review of the applicable materials and are held to a reasonable degree of medical and scientific certainty. I reserve the right to amend my opinions and this report upon the receipt of records, material or other information, including but not limited to any future tests and clinical evaluations.

II. General Opinions

My opinions that follow apply to the following Ethicon's meshes for pelvic organ prolapse repair.

a. Reaction to Mesh

A biocompatible material is one that, when implanted into the human body, performs the function it was designed to do without causing significant dysfunction. It does not mean there is no reaction to the material at all. The implantation of a foreign body, including a biocompatible medical device, initiates the body's inflammatory and foreign body responses, as discussed below.

Various inflammatory responses are known to be associated with synthetic mesh implantation into pelvic tissues. Not surprisingly, most of the data on the acute response to implantation of meshes is derived from experimental animals where the mesh was placed with the intention of observing the tissue response at various intervals of time.[1,2,3,4] Acutely the mesh fibers are enveloped by fibrin and other blood and tissue proteins as well as a modest amount of acute inflammatory cells. In the sub-acute period, a mild to moderate histiocytic cellular response is seen, accompanied by a variable amount of foreign body type giant cells in close proximity to the mesh fibers. In this sub-acute time period, ingrowth of connective tissue elements such as blood vessels, nerves, and accompanying connective tissue collagen is noted between the mesh fibers, the so-called "pores".

In the chronic phase, collagen fibers become denser and more abundant, forming a fibrous connective tissue with a scant chronic inflammatory infiltrate.[5,6,7] This fibrous connective tissue is necessary for the proper function of pelvic organ prolapse repairs and

acts as a support for previously weakened tissue in prolapse patients. Without additional support, these patients would continue to suffer from prolapse, a condition, which for many, is debilitating. The chronic inflammatory cells seen in histology slides are not by themselves an indication that these cells are engaged in producing bioactive agents of inflammation such as cytokines or free radicals. In the chronic stages of inflammation, these cells are usually quiescent and intricately regulated by the body.[8]

Chronic inflammation is a finding seen in the vaginal tissues of women who suffer from pelvic organ prolapse, stress urinary incontinence, and pelvic floor dysfunctions even before surgical implantation of mesh. These conditions are typically caused by the stressed, stretched, or thinned tissue of the pelvic diaphragm. Such damaged tissues always will contain chronic inflammatory cells. Even in women who do not have SUI, pelvic organ prolapse, or other pelvic floor dysfunctions, the fibrous connective tissue that is present throughout the body, including in the lower genital tract, contains chronic inflammatory cells. The presence of modest amounts of inflammatory cells in these tissues should not be equated with significant injury to that or other tissues, but rather a response to normal, everyday stress.

Surgical procedures, including mesh implantation, necessarily cause tissue injury leading to wound healing. Factors other than the implants themselves affect the process of healing the surgical site. It is well known that body habitus, in particular obesity and diseases such as diabetes and blood stasis, can delay wound healing. Similarly, acquired behaviors such as cigarette smoking also can adversely affect the rate and quality of wound healing. Finally, one of the most influential factors that may adversely affect wound

healing is infection where bacterial toxins and the corresponding inflammatory response can cause wound delay or wound closure failure.

Large pore meshes such as the Prolene Soft used in the Prolift products allow for the ingrowth of blood vessels and other connective tissue elements, as well as chronic inflammatory cells, into and around the pores of the mesh material.[9] This ingrowth provides additional physical support to the mesh that is necessary for the long-lasting effect responsible for the relief of pelvic laxity. In addition, large pore, monofilament meshes have been clinically shown to have low rates of infection,[10,11,12] due to the properties of the mesh that allow the type of tissue ingrowth that permit the body's defenses to combat infection.

In the case of the Prolene Soft mesh used in Prolift procedures the findings in the literature describe that explants from these meshes display an appropriate fibrous tissue reaction with scant amounts of chronic inflammation. A mild foreign body reaction is occasionally mentioned, although not as a major feature of the specimen.[13,14,15] The tissue reaction to the Prolift is indicative of a biocompatible implant. Even though the body reacts to mesh by eliciting scant chronic inflammation, scattered foreign body giant cells, and increased fibrous tissue immediately adjacent to the mesh material, that reaction does not adversely alter the physiology of the patient. The only physical alteration in the majority of patients is the function the mesh was designed to perform: to support the prolapsing anterior or posterior compartment, thus reducing pelvic organ prolapse and its symptoms. The studies that have looked at the tissue reaction to Prolene or Prolene Soft mesh in the human vagina support these findings.[16,17,18,19]

This biocompatibility is borne out by my own experience as pathologist as well as the clinical data showing improved results in the efficacy of pelvic organ prolapse repair using polypropylene mesh compared to prior surgical techniques.[20] This benefit was seen while maintaining complications at a modest rate.[21,22] The Prolene material itself is supported by decades of safe and effective use as a suture and in hernia mesh applications, as well as nearly two decades of use in stress urinary incontinence.

b. Clinical Pathological Correlation

Pathology findings can sometimes be equated to clinical signs and symptoms. In these instances, a body of knowledge accumulated by analyzing large bodies of evidence must be established to serve as proof that these findings are causative of a patient's symptoms. For example, when a pathologist finds cancer destroying a patient's bone she or he can state with a high degree of certainty that the fracture that the patient suffered was due to a metastasis as cancer is usually not present in bone, cancer is replacing the well-known sturdy structure of the bone and a fracture is present at that site. In addition, a large body of experience shows that when a metastasis exists in a bone, then that bone more likely than not will fracture in time. When there is no body of evidence that a pathological finding predicts or equates to clinical findings, then a clinical pathological correlation cannot be made with any degree of certainty. In the case of equating histological findings found in mesh explants to the sensation of pain, there is no body of evidence supporting that any given finding unequivocally predicts pain. To be able to determine if a pathology finding equates to the sensation of pain, the finding would need to be limited exclusively to those patients experiencing pain and not found in patients who do not feel the sensation of pain. There is no published experience reporting such data.

There is no body of evidence establishing histologic findings of transvaginal meshes, much less the Prolift meshes, that equate to any patient symptomology. In my experience as a pathologist examining explanted mesh specimens, the findings in cases where the patient had no symptoms of pain were identical to the findings described by Dr. Iakovlev, who serves as an expert for many plaintiffs in this litigation, in his plaintiff-patient population. In addition, in the only peer reviewed article attempting to correlate histology findings from explanted mid-urethral slings with clinical symptoms of pain, the authors found they could not correlate the two.[23] Dr. Iakovlev acknowledges a similar lack of clinical pathological correlation in his own recently published article, where he stated "when microscopy was performed, results of the microscopic examinations usually did not explain the specific complications experienced by the patients."[24] Finally, Dr. Iakovlev himself acknowledged that a sufficient body of evidence does not yet exist to correlate the histology findings of mid-urethral slings and symptomology: "At present, general human tissue interactions with the mesh are known, but we have an incomplete understanding of interactions specific to a mesh material and design as well as the pathophysiology of any complications."[25] The same is true for pelvic organ prolapse meshes.

III. Response to Opinions of Plaintiffs' Pathology Expert

a. Dr. Vladimir Iakovlev's Opinions

i. General

I have had the opportunity to review the opinions rendered by Dr. Vladimir Iakovlev contained in his Wave 1 report, several of his other reports in Ethicon cases, and his deposition and/or trial testimony in the Bellew, Corbet, Edwards, Mullins, Carlino, and Ramirez cases. As it pertains to the field of Gynecological Pathology, I find that several of Dr. Iakovlev's opinions are not generally accepted by the medical community as valid, scientifically proven, or even probable. Other of his statements and theories are demonstrably false, as discussed below.

The modest rates of complications in patients who have had pelvic organ prolapse repair with Prolift are completely absent from Dr. Iakovlev's opinions and testimony. He fails to discuss specific complication rates in any fashion in his reports. This is of utmost importance because he presents no data or histologic evidence regarding the majority of patients who not only suffer no adverse effects of the Prolift procedure but who are also cured at high rates.[26,27,28] Dr. Iakovlev cannot reliably comment on clinical findings without any discussion or recognition of the complication rates. Without any discussion of rates, Dr. Iakovlev's admittedly "small cohort" could be a few cases out of one million, yet he attempts to extrapolate these findings to all women implanted with Prolift.

I am a reviewer for several of the leading peer reviewed journals in the field of Obstetrics, Gynecology and Pathology. I am well aware of the scientific methods necessary to establish causation. Observations of morphological changes in tissue such as those reported by Dr. Iakovlev need to be compared with a control population to reliably

draw a clinical correlation. This would require evidence of the histology seen in women who did not have the symptoms in question. Without such control comparisons, a clinical correlation is mere speculation and not scientifically grounded. For example, when the same histologic findings are seen in a population of women suffering no symptoms of pain and those with symptoms of pain, these histologic findings cannot be claimed to be the cause of pain. Moreover, as here, when there is no body of evidence demonstrating histology is associated with clinical symptomology, clinical pathological correlations cannot be made.

Dr. Iakovlev's 2015 review article and his current expert report fail to cite an important paper that bears directly on his theories. Dr. Iakovlev states that "[a]fter >50 years of use, only a few published studies exist in which investigators actually examined histological changes in mesh explants that had been removed from humans."[29] Those "few published studies" he cites for support are composed only of three hernia mesh papers from other plaintiffs' experts in this litigation and a paper looking at mesh from a single patient. Dr. Iakovlev does not cite Hill's paper that looked at more than 100 explanted mesh slings and found that complaints of pain were not associated with increased inflammation and that fibrosis was consistent between the group with patients who had complained of pain and the group with patients who had no complaints of pain.

The theories that Dr. Iakovlev claims to state to a reasonable degree of medical certainty in his expert reports are not asserted with this level of certainty in his recent peer reviewed publication in Nature Reviews. This fact alone demonstrates that his theories are not generally accepted and, after being subjected to peer review, were substantially diluted and made uncertain. Most notably, Dr. Iakovlev's recent publication notes: "however,

when microscopy was performed, results of the microscopic examinations usually did not explain the specific complications experienced by the patients" and "[a]t present, general human tissue interactions with the mesh are known, but we have an incomplete understanding of interactions specific to a mesh material and design as well as the pathophysiology of any complications."[30] This is consistent with Hill's findings and my own clinical experience. Furthermore, Dr. Iakovlev's apparent reluctance at his deposition in the Mullins case to attribute findings from his pathology photomicrographs to clinical symptoms demonstrates that there is not a sufficient body of evidence to link histology findings with Prolene mesh to the clinical symptoms that occur at low rates.

ii. Anatomy

Dr. Iakovlev shows a lack of understanding of the female anatomy and physiology, particularly where he asserts that smooth muscle of the vaginal wall is responsible for contraction of the vagina during intercourse.[31] This is false. Contraction of the vagina during intercourse is a mechanism of the striated musculature of the pelvis, including the pubococcygeus and bulbospongiosus.[32] In the female, these muscles are small, almost vestigial in function, and certainly would not have the strength to apply significant tension to an implanted mesh, contrary to the statement Dr. Iakovlev makes in his report.[33]

Dr. Iakovlev testified at his deposition in the Mullins case that the presence of smooth muscle in the pore space shows the mesh is migrating into the smooth muscle. He asserts this is true because smooth muscle has a very limited ability to regenerate or regrow after injury. This is false. Smooth muscle is able to regenerate in response to injury, such as surgery.[34] This is a generally accepted fact. Thus, the presence of smooth muscle in the

pores is not evidence of migration, but instead shows pre-existing tissue elements can access the macroporous Prolene mesh.

Dr. Iakovlev's statements that the presence of smooth muscle in the mesh explants causes organ dysfunction is speculative and lacks any scientific support.[35]

In addition, Dr. Iakovlev theorizes that the "female genital area" has much higher nerve density than abdominal areas.[36] First, he does not identify this area, which is problematic because areas such as the cervix have very little innervation.[37] Second, the vaginal wall is not particularly well innervated, particularly in comparison to the vulva and the introitus of the vagina.[38]

Dr. Iakovlev asserts the implantation site for transvaginal mesh is a "critical anatomical location." I have the following comments on this section of his opinion:

- Dr. Iakovlev states that the mesh cannot be placed parallel to the organs that course the pelvic diaphragm. This is an incorrect statement. When a midureutrhral sling is placed, the sling is placed parallel to the urethra. The plane of the mesh conforms underneath the cylindrical urethra. Similarly, when a posterior organ prolapse "rectocele" is corrected using transvaginal mesh, the mesh is placed over the prolapsing rectum in a fashion where the plane of the mesh is parallel to the anterior wall of the rectum. The same is true when an anterior pelvic organ prolapse "cystocele" is repaired where polypropylene mesh is placed in a plane parallel to the posterior bladder wall. Although no anatomical structure, such as the abdominal fascia, exists in the pelvis, the presence of pelvic

connective tissue is invariably present between the mesh and the organs mentioned above in a properly implanted mesh.

- Dr. Iakovlev states that placement of the mesh through a "contaminated field and mesh exposure" provide routes for infection. The rate of infection following pelvic organ prolapse repair with polypropylene mesh is very low, and is comparable to or lower than any surgery performed in other anatomical areas such as thoracotomy, laparotomy which do not course through a contaminated field and do not introduce synthetic material into the operative field. These data demonstrate that introducing polypropylene mesh does not increase the risk of infection from performing the surgery.
- Any surgery to correct pelvic organ prolapse, even in the absence of mesh, will interrupt the innervation and blood supply to the vaginal mucosa. Insertion of a large pore mesh material allows for the regrowth of the vascular supply and innervation to the area. The implantation of mesh does not interfere with the innervation or vascular supply of either the bladder or rectum as the nerves and blood vessels that supply these organs follow a route that is distant to the anatomic location of the mesh.

Dr. Iakovlev also states that excision of mesh cannot restore the preexistent tissue state. In women who undergo either midurethral sling placement or transvaginal mesh to repair pelvic organ prolapse, the preexisting state is abnormal and causes symptomology that drives the patient to surgical repair. Any surgical repair of these conditions relies on scarring to relieve the primary pathology of the tissues (pelvic laxity).

iii. Scarring and Pain

There are several inconsistencies in Dr. Iakovlev's claims regarding scar tissue. Dr. Iakovlev attempts to contrast scar tissue without mesh and the tissue found in and around mesh. He claims "[b]y contrast, mature scar tissue after non-mesh surgeries . . . can remodel with time . . ."[39] However, earlier in his report Dr. Iakovlev claims that the tissue in and around the mesh pores undergoes contraction and remodeling.[40] These two statements are contradictory and inconsistent. In addition, Dr. Iakovlev's theories suffer from the following problems:

- Dr. Iakovlev's theories regarding mesh stiffening are not supported by any data. Palpation of formalin fixed tissues in small specimens is not a reliable method to discern whether that tissue exhibited increased stiffness *in vivo*.
- Dr. Iakovlev claims that mature scar tissue after non-mesh surgeries does not show inflammation.[41] This is incorrect. It is well known in pathology, and is something I teach my students and pathology residents, that scar tissue can contain chronic inflammation.
- Dr. Iakovlev's assertion that there are traumatic neuroma-like lesions in the explants of polypropylene mesh is not supported by the images found in his report. All of the examples depicted in his images can be explained by artifacts of fixation and processing and do not meet the definition of traumatic neuroma. Importantly, not a single example of a traumatic neuroma is present in those tissues.
- Dr. Iakovlev states "that the female genital area has much higher nerve density compared to the midline anterior abdominal wall and the groin." A statement for which he provides no data. He goes on to state that placement of vaginal mesh is

associated with higher risk of chronic pain than placement of mesh for hernia repair, either ventral or in the groin. This statement is contradicted by the published reports studying pain in patients following these surgeries. In Dr. Iakovlev's own publication, he states that reported incidence of post-herniorrhaphy pain has been documented to be 28.7–75.5 % following anterior open repairs.[42] This percentage is far higher than reported data in the vaginal mesh literature.

1. Compartment Theory

Dr. Iakovlev's opinion relies heavily on his theory of a mesh "compartment" or a "compartmentalization" caused by transvaginal mesh in the tissue. In addition to a lack of any data or support on this subject, geometry does not support Dr. Iakovlev's theory. At most, Prolene Soft is 0.8 mm thick. Given that the pore spaces are essentially holes, Ethicon's pelvic organ prolapse meshes are no more a compartment than is a fishing net.

- Regarding edema, Dr. Iakovlev asserts that "pain due to swelling is present in cases of inflammation and trauma and the effect is amplified in rigid compartments."[43] This theory is speculation and lacks any support. Edema, as Dr. Iakovlev recognizes, is due to an accumulation of fluid. Any fluid imbalance would easily escape through the mesh pore, just as water would pass through a fishing net, as those spaces are completely open in the mesh structure.
- Nerves, vessels, and other tissue elements grow through the pore space, which is essentially a two dimensional object in the three dimensional space of the tissue. Such a structure cannot possible create the enclosed compartment that Dr. Iakovlev posits in his report.[44] Dr. Iakovlev has no scientific support for his compartment theories.

2. "Scar Plate" or "Fibrotic Bridging"

Dr. Iakovlev posits "the mesh designs that are currently used for transvaginal devices, including the Prolift line of products and the TVT line of products, show a continuous scar plate that encases all of the mesh filaments and spans across nearly all of the pores."[45] He provides two citations for this proposition, neither of which support his opinions in this case.

Dr. Iakovlev describes scar plate and/or bridging fibrosis as scar "span[ning] or bridges across the pores."[46] Dr. Iakovlev also provides figures as examples of this phenomenon, but the figures purporting to demonstrate scar plate and/or bridging fibrosis show granulomas – if present at all -- immediately in contact with the mesh fibers, with intervening connective tissue containing blood vessels and nerves. Dr. Iakovlev's figures show pore spaces with integrated connective tissue, which is the expected finding in functional, large pore mesh. The presence of fibrous tissue shown in Figure 2b is an expected finding when adipose tissue is injured and then repaired. The mesh found within that fibrous tissue shows minimal inflammation and the interaction of the mesh fibrous tissue complex is in close apposition with normal adipose tissue, thus showing its biocompatible nature.

The AMS silicone study cited by Dr. Iakovlev specifically notes that Ulmsten pioneered a sling device with minimal complications. That device became the TVT.[47,48] It is unclear how this supports Dr. Iakovlev's statement.

3. Erosion

Dr. Iakovlev's statement that mucosal erosion is a complication unique for mesh surgery is incorrect.[49] Slings made from autologous fascia have been reported to cause mucosal erosion.[50]

4. Pain

As previously mentioned, I have had the opportunity to examine over 50 explanted mesh specimens both grossly and microscopically in the past 22 years at USC. Approximately twenty of these samples were removed for urinary obstruction, where the suburethral sling was placed under excessive tension during surgery and obstructed the urethra. To my knowledge, none of these women were experiencing pain. Other samples were removed in surgical procedures to revise ineffective slings, where less than optimal surgical placement of the sling made the procedure ineffective. These women did not report pain as a reason for their revision. A small fraction of the samples were removed for mesh exposure or erosion. In these instances patients experienced the discomfort of mesh rubbing against their vulva but rarely, if ever, pain. In all of these samples, despite the fact that these patients were not suffering from any pain, I observed the identical histological changes that are found in the photomicrographs and slides that Dr. Iakovlev relies upon to claim these are causative of pain in the patients involved in this litigation. I have described these findings earlier in my report. Recently, I have had the opportunity to examine mesh specimens explanted from patients with pelvic organ prolapse. The histological changes present, as related to the mesh, are identical, even if the types of tissue present in the near vicinity of the mesh differ. These differences are due to the anatomical location of the mesh implants where distinct tissue types, such as adipose tissue, are common. Again the varied

tissue types are almost universally similar in histological appearance when compared to women with pelvic laxity.

Furthermore, by Dr. Iakovlev has written that pain occurs in only a small cohort of patients. If the tissue reaction to mesh caused the pathology that Dr. Iakovlev claims in all specimens examined, then the consequences would be uniform across most, if not all patients not just a small cohort.

Dr. Iakovlev presents numerous theories and observations regarding nerves, most of which are misplaced and largely incorrect.

- As discussed previously, Dr. Iakovlev's opinions regarding the degree of innervation in the vagina are incorrect and not supported by the scientific and medical literature.
- Dr. Iakovlev's claim that nerve deformity in the samples he evaluated is responsible for pain is without basis. Dr. Iakovlev has no basis to assert that the nerves seen in his specimens are abnormal. Differences in tissue shrinkage when exposed to formalin fixative can account for most of Dr. Iakovlev's findings regarding nerves in the explanted mesh samples. These differences can artifactually cause the shape of the nerve to lose its normal circular or cylindrical appearance. In photographs showing immediate apposition of nerve to mesh fiber, the nerve itself shows no degenerative changes and likely represents a nerve closely passing by a mesh fiber. The complete absence of inflammation in these photographs attests once again that there is no adverse effect to the nerve. In any event, identification of irregularly shaped nerves in no way indicates that these

nerves are compromised and/or damaged and clearly would not mean that they would produce the sensation of pain. Furthermore, the nerves contained in Dr. Iakovlev's photomicrographs are not concerning. Neither Dr. Iakovlev's methods nor his theories are generally accepted in the fields of gynecologic pathology or surgical pathology.

- Dr. Iakovlev's figures where he purports to show nerve degeneration are inconclusive. In Figure 3h (bottom panel), he shows S100 positively stained elements with a center portion that is unstained. Dr. Iakovlev's opinion fails to account for the fact that nerves consist of more than simply axons and myelin sheath; they have other structures, some of which do not stain positively for S100, such as Renaut's bodies.[51] Dr. Iakovlev also fails to rule out the effects of fixation on antigen reactivity as a potential cause of the internal space of the nerve that is not s100 positive.
- Dr. Iakovlev uses an unreliable and incorrect correlation between nerves found in scar tissue and pain. Nerves found in scar tissue do not equate to pain. Scar tissue is typically innervated but patients do not commonly report pain in their scars. In addition, Hill and colleagues found there was no correlation between degree of fibrosis and the sensation of pain in mid-urethral slings.[52]
- Even if Dr. Iakovlev were correct about deformed or abnormally appearing nerves, he has identified no sensory receptors necessary to reliably conclude that a given nerve fiber will transmit pain signals. Dr.

Iakovlev also states that inflammation can make a person more susceptible to pain. It is unclear as to whether Dr. Iakovlev is referring to stimulation of these nerves or other mechanisms of pain caused by inflammation. Even so, the published histological data on SUI slings does not support that this occurs in the presence of mid-urethral slings. In fact, Hill found slightly more inflammation in patients complaining of no pain than those who complained of pain.[53] This absence of correlation is consistent with explanted meshes I have examined in my practice. It also is consistent with my opinion that the presence of chronic inflammatory cells seen on histology slides is not indicative that a deleterious effect is occurring, that the cells are activated, or that they are causing a painful response.

- Thromboses and/or occlusions of capillaries and/or small arterioles are commonplace throughout the body and have never been shown to be associated with pain.

In addition to specific comments, Dr. Iakovlev brings up several other seemingly random topics throughout his report and image caption. I address these here as they again lack scientific basis:

- Figure 9a The photographs in both panels highlight a blood vessel that has undergone thrombosis, fibrosis, but where recanalization has not occurred. Absence of recanalization is indicative of a complete interruption of that blood vessel. Such an interruption would only occur at the time of the surgery where the mesh was placed.

- Figure 9b(1) both panels also depict a thrombosed, not recanalized, fibrotic artery, which would indicate complete transection. This event is likely to have occurred at the time of mesh insertion.
- Figure 9b(2) purports to show thrombosed capillaries. Each photograph depicts a small capillary containing fibrin but abundant blood in the lumen. The findings are inconclusive evidence of thrombosis.

iv. Structural changes

As discussed below, Dr. Iakovlev's theories regarding structural changes of the mesh are not supported by reliable scientific evidence.

Dr. Iakovlev opines that transvaginal mesh curls and folds in vivo. The evidence he relies upon regarding explanted specimens contains artifacts of excision and fixation, which make them artifactual rather than the *in vivo* condition of the mesh. For example, elasticity of the vaginal, retropubic, and pelvic floor tissues will immediately cause an excised specimen to contract. This is caused by the natural elasticity of the tissue imparted to it by the high elastin content. In addition, formalin fixation will cause excised tissue to further contract due to the cross-linking of proteins and collagen. The contraction of tissues is not uniform and certainly different from the non-contractile Prolene mesh, resulting in curling and folding outside the body. Furthermore, Dr. Iakovlev has testified at deposition in cases involving both Ethicon's TVT and Prolift that he cannot tell whether curling and other mesh deformations occurred during surgical placement or *in vivo*.[54] His opinions attributing any deformation to the mesh are therefore unreliable and without basis.

v. Degradation Theories

1. Lack of Evidence

Dr. Iakovlev focuses much of his report on degradation theories. However, Dr. Iakovlev's recent publications on the topic are much less certain. For example, he recently stated that "the question of whether polypropylene degrades *in vivo* has not been fully resolved . . ." Dr. Iakovlev also allowed that "[a] lack of published studies exists in this area, although the limited evidence suggests [oxidative degradation]."[55] However, Dr. Iakovlev asserted in his expert report in Mullins that "the amounted body of evidence has reliable proven that polypropylene, including Prolene, degrades when exposed to the environment of [the] human body."[56] Suggestion and questions that have "not been fully resolved" do not allow for positive findings to a reasonable degree of medical certainty that degradation of polypropylene occurs *in vivo*. Dr. Iakovlev's uncertainty in peer-reviewed publication is inconsistent with his certainty in this case. The scientific method requires much more than suggestion and questions, which are no more than unproven hypotheses. Once again, in his most recent report, Dr. Iakovlev acknowledges this by having removed the statement that the body of literature supports degradation of polypropylene in the human body.

In addition, Dr. Iakovlev's theories of "degradation" are problematic, unsupported, and speculative as discussed below:

- Despite his now deleted assertion that the body of evidence shows Prolene degrades in vivo, many of the articles Dr. Iakovlev cites for degradation involve substances that are not Prolene and in applications completely outside the vaginal tissue in which transvaginal mesh is implanted.

- He makes the statement that "Loss of mechanical properties was shown in explanted meshes", and cites for support an article in Fibres and Textiles in Eastern Europe on polypropylene fiber – not mesh -- degradation by artificial light and sunlight.[57] Artificial light and sunlight are two conditions wholly inapplicable to transvaginal mesh, which is implanted in the human vagina. Dr. Iakovlev provides no reliable evidence that degraded mesh loses it mechanical properties.
    - Dr. Iakovlev has testified recently in the Mullins case that the mesh core beyond the "bark" layer appears unaffected and the physical properties unchanged.[58] He also testified that the layer is no thicker than 5-6 microns for Prolene in SUI meshes. Dr. Iakovlev has offered no support regarding changes to the physical properties of the mesh under these conditions.
- Large portions of his opinions on degradation are neither pathology opinions nor supported by science or referenced by Dr. Iakovlev. For example, Dr. Iakovlev states that "[c]racking also indicates that there are internal forces acting to shrink and deform the material."[59] This is speculation and is not based on reliable science. Dr. Iakovlev offers no engineering principles or polymer chemistry theories to support this far-reaching opinion, and nothing in pathology would permit such a conclusion.
- In a prior report, Dr. Iakovlev posited that "[i]n relation to clinical symptoms, degradation leads to additional stiffening and late deformations of the mesh, independent of scar contraction discussed below."[60] In that report, he failed to fill in the mechanistic steps required of a scientifically valid theory and he provided no support for this statement. Without any support, this statement was pure

speculation. Dr. Iakovlev appears to acknowledge this failure in his current report, where he now says degradation "needs to be considered as a factor of" rather than "leads to" additional stiffening.[61] Albeit, he continues to assert that the mesh demonstrates stiffening and late deformation, two allegations for which there is no reliable scientific evidence. Furthermore, as discussed previously, Dr. Iakovlev has testified that he does not know whether the deformations for which he purported to provide photomicrograph examples occurred at placement or due to *in vivo* changes.

- Dr. Iakovlev states that the degradation bark stains with both Hematoxylin and Eosin, giving it a color half-way between the staining characteristics of these dyes. He states that the degraded nature of the polypropylene "traps" the stain into "nanocavities" of the degraded polypropylene granting it its staining characteristics.[62,63] In his article, Dr. Iakovlev offers no scientific support for this theory. Histology stains are designed and used by pathologists to stain biologic tissues and cells. Stains such as H&E work by attaching to structures with different ionic charges.[64] They are not trapped like a cup would hold water. As a result, the methodology of identifying degraded polypropylene using stains for biologic tissue is not accepted by the majority of experts in the field.
- In addition, Dr. Iakovlev's stain trapping theory does not account for the smaller cavities on the inner "bark" staining with the same intensity as the larger cavities on the outer portion of the "bark". His figures show uniformity of staining using H&E, which would not occur if the stain were merely becoming trapped in cracks.

- Dr. Iakovlev's methodology does not reliably rule out that the band of material around the Prolene fibers in the tissue samples is polypropylene that degraded as an artifact of tissue processing rather than *in vivo*. Polypropylene is known to be incompatible to xylene exposure and increased temperatures that occur during tissue processing.[65]
- In response to Dr. Iakovlev's theory, Ethicon's expert, Dr. Steven MacLean, has intentionally oxidized Prolene mesh, processed it using standard tissue processing protocols, and attempted to stain it with H&E. The findings from these experiments show that intentionally oxidized Prolene does not take up stain as Dr. Iakovlev posits. Dr. Iakovlev previously testified that tests were underway to intentionally oxidize polypropylene and attempt to stain it.[66] Dr. Iakovlev does not offer the results of such attempts in his report. Dr. Iakovlev testified in the Mullins case that he will not remove and visually analyze the Prolene he intentionally oxidizing after it has been in the allegedly oxidizing solution for 1.5 years.[67] This is important because oxidation is the physiological mechanism Dr. Iakovlev asserts leads to the degradation of Prolene.[68]
- Dr. Iakovlev posits that macrophages secrete substances (Reactive Oxygen Species) that degrade the mesh material.[69] Although macrophages can at times secrete free radicals and other chemicals in an attempt to digest materials, there is nothing in the explanted specimens that I have examined – or in the photomicrographs Dr. Iakovlev included in his expert report -- to indicate such a process has occurred. Not all of the mesh fibers have macrophages or giant cells associated with them. Even where giant cells or macrophages are present in close

association with the mesh fiber, little if any inflammation is present. If macrophages were causing oxidative damage to Prolene, those same substances would cause tissue destruction that would result in necrosis and abundant acute and chronic inflammation. Lack of these findings in Dr. Iakovlev's photomicrographs is proof that such a process is not occurring to any significant degree.

  - Dr. Iakovlev also recently testified in the Mullins case that he examined mesh specimens and found no bark. Even in those cases, the explants showed an inflammatory reaction.[70] Dr. Iakovlev's theories do not account for this.

- Dr. Iakovlev claims that all the fibers are degraded as evidenced by the hallmark morphologic finding of "bark". It is highly improbable that if Prolene fibers were to degrade that they would degrade uniformly throughout all of the fibers in a specimen. If the macrophages and/or giant cells were the mediators of this degradation, one would expect to find more degradation (a thicker bark) in fibers associated with these cells, which is clearly not the case. For example, see Figures 13a and 13h of Dr. Iakovlev's report, which purport to show a "degradation bark" adjacent to several layers of fibroblasts, with no macrophages near the vicinity.[71]
- Many of Dr. Iakovlev's photomicrographs fail to show the presence of any inflammatory cells or macrophages surrounding the fibers. The tissue immediately adjacent to the fibers in these pictures instead contains fibroblasts and collagen, but none of the cells that Dr. Iakovlev posits cause degradation of the mesh fibers. This is consistent with my clinical experience.

- Dr. Iakovlev acknowledges that the degradation bark plateaus, and his data show that occurs at 4-5 microns.[72,73] Yet, he proposes no mechanistic theory to account for such a cessation.

2. No Clinical Significance

Even if Dr. Iakovlev's "bark" were evidence of mesh degradation *in vivo*, there is no evidence showing any clinical significance of this finding.

- Prolene mesh explants contain little inflammation, no signs of tissue damage, and no other indicators of a deleterious process occurring in the immediate vicinity of the mesh.
- As stated previously, many of the photomicrographs showing "degradation bark" in Dr. Iakovlev's report are surrounded by connective tissue with no inflammatory cells, macrophages, or foreign body giant cells. Absence of these cells indicates that the bark is not eliciting the inflammatory reaction Dr. Iakovlev posits as a cause of clinical effect.
- Plaintiffs' expert Howard Jordi, Ph.D., has previously testified that the Prolene cracking he has seen is only one micron thick.[74] There is no scientifically reliable support that this has any clinical effect. The tissue reaction to Prolene mesh does not support any clinical effect of this one micron layer.
- Even if *in vivo* degradation of Prolene were true, Dr. Iakovlev acknowledges that further studies would be needed in order to draw associations between that degradation and the development of complications.[75]

vi. Additional Comments for Dr. Iakovlev's Photomicrographs

- Figure set 1a -- images selected represent the most severe example of the foreign body reaction. Even though it is the most severe, it is still limited to the immediate 100-200 micron radius around the fiber. Loose connective tissue, which is identical to normal vaginal submucosa, is present a short 500 microns away.
- Figure set 1b – see comments to 1a. In addition, there is a designation of "scar" to fibrous connective tissue that does not meet that definition, including a label of "scar" on top of a blood vessel.
- Figure set 1c – is an extremely limited view of the tissue and is limited to the immediate proximity to the mesh fiber, where dense fibrosis is an expected and desired reaction.
- Figure set 2a – same comment as 1a. Tissue 100 microns away from the fiber is normal.
- Figure set 2b – Designation of fibrous (scar) encapsulation is incorrect. The tissue indicated by the arrows represents dense connective tissue but not scar. The desired outcome when reinforcing weakened prolapsing tissue is to strengthen it by providing not only a scaffolding (mesh) but by increasing the content of dense, supportive connective tissue in order to correct the laxity of the previously defective tissue.
- Figure set 2c – The extremely low magnification of this photograph makes it difficult to appreciate that the areas in between the fibers clearly does not represent scar as they contain normal capillaries (blood vessels).

- Figure set 2d – Designation of scar to areas of dense but organized connective tissue is incorrect. Note that in areas designated as adipose tissue (fat), completely normal fatty tissue is present a few hundred microns aware from mesh fibers. It is important to remember that normal pelvic tissue contains adipose tissue as well as denser fibrous tissue, smooth muscle and ligaments. It would be impossible to distinguish some of these normal tissues, particularly dense connective tissue or ligaments, from the areas designated as scar in the photograph.
- Figure set 2e – same comment as 2d. The term "scar plate" referring to the longitudinal presence to the mesh material in the center of the photograph does not make biological sense. The longitudinal mesh material in the center of the photograph is almost unquestionably a series of longitudinally cut mesh where no pore would be expected. Hence, not indicative of the term "scar plate" as defined by Klinge and his colleagues when referring to smaller pore meshes than Prolene mesh.
- Figure set 2f – the designation of scar in this sample is again incorrect. Even in this low magnification it is evident that the architecture of the connective tissue is purposeful (arranged in bundles) which by definition would not be scar. This purposeful architecture represents connective tissue with purposeful support roles.
- Figure 2g – In the top panel, the areas designated as bridging fibrosis are again incorrect, as proven by the presence of normal smooth muscle in those areas as evidenced by the stain for smooth muscle in panel b. Scar or bridging fibrosis does not contain smooth muscle.

- Figure set 3a – The upper panel depicts three mesh fibers with an adjacent nerve fiber. The nerve fiber looks normal in appearance. Although it is curved, one cannot exclude that formalin fixation is responsible for the curvature as nerves contract at a different rate than surrounding connective tissue. The foreign body response is limited to less than 100 microns around the mesh fiber. There is no inflammatory infiltrate in proximity to the nerve. The nerve and mesh fibers are separated by a thin layer of fibrosis. In the bottom panel, the presence of nerves that appear histologically normal in between areas where fibers are encountered indicate the restoration of normal connective tissue, which is the expected and desired effect of a large pore mesh. Attributing clinical symptoms to these findings is not possible.
- Figure set 3b – Of the two nerves depicted in this image, indicated by arrows, only the one encircling the mesh fiber shows any evidence of abnormality. The other is completely normal. Proximity of a nerve fiber to mesh does not indicate nerve injury. There is no inflammation or morphologic changes suggestive of nerve damage. It would be impossible to determine from morphology alone whether this is a functioning nerve fiber. Attributing clinical symptoms to these findings is not possible.
- Figure set 3c – The nerves in this image show no evidence of deformation. The nerve present in the upper left-hand portion of the photograph sits adjacent to loosely fibrous alveolar connective tissue.
- Figure set 3d – In the upper panel, represents a nerve that surrounds a mesh fiber, showing no signs of pathologic change. Furthermore, the presence of ganglia

associated with these nerves indicates that the nerve is autonomic in nature and does not transmit pain sensation. The photograph in the lower panel depicts S100 (not H&E) positive nerve tissue. There is no scar in between the nerve tissue and certainly by definition this is not a traumatic neuroma. The definition that "separation of fascicles in the scar tissue = traumatic neuroma" is incorrect.

- Figure 3e – The definition of a traumatic neuroma is a mass composed of nerves with axonal sprouting and surrounding perineural fibrosis. The photograph depicted in the top panel photo does not form a mass, does not contain axonal sprouting, and does not depict significant perineural fibrosis. The bottom panel again fails to depict any of the features that define traumatic neuroma. The nerve most adjacent the mesh fiber abuts a thin fibrous layer around the foreign body giant cell reaction surrounding the fiber. There is no inflammatory response indicating any damage to this nerve fiber.
- Figure 3f – The images depict a normally appearing nerve with no morphologic abnormality and no inflammatory response to indicate any damage.
- Figure 3g – The nerves depicted in the upper panel contain ganglia and are therefore autonomic, precluding them from transmitting sensation of pain. The lower panel again shows nerves that fail to meet any of the criteria for a traumatic neuroma.
- Figure 3h – The bottom panel shows S100 positively stained elements with a center portion that is unstained. The findings may be consistent with a Renaut body. These are not indicative of chronic nerve trauma or entrapment. The top panel

shows a nerve with separation of the S100 positive material, a finding that does not equate to nerve degeneration.

- Figure 4a – Agree there are nerves containing ganglion cells. These indicate they are autonomic in nature.
- Figures 4b, c, d, e – same as above in 4a. There is no indication that this nerve is affected by the mesh.
- Figure 5 – The figure depicts a normal pattern of innervation of the vaginal submucosa, most of which is autonomic in nature.
- Figure 6a – Photographs depict blood vessels of a caliber that can be found in normal vaginal submucosa. There is no indication that these blood vessels are dilated. The designation of the area on the lower left as edematous scar is incorrect. The area demonstrates normal loose connective tissue.
- Figures 6b and 6c – Vessels depicted in upper panel are of a normal caliber for vaginal submucosa and show no evidence of dilatation. There is no evidence or edema in either the upper or lower panel. The tissue represents normal, loose connective tissue.
- Figure 6d –Vessels depicted in upper panel are of a normal caliber for vaginal submucosa and show no evidence of dilatation. There is no evidence or edema in either the upper or lower panel. The tissue represents normal, loose connective tissue. In the lower panel, the magnification is too low to identify the structures indicated by the arrows. I have never read or heard of the pathology term "fluid bubble" in tissue and would not be able to comment on them. However, there is no evidence of edema in this tissue.

- Figure7a – Photograph depicts mesh material adjacent to various connective tissue elements. Striated muscle is present in areas of the pelvic diaphragm that is affected by laxity and repair of this area using mesh could result in these findings. There is no significant inflammation associated with the striated muscle to indicate an adverse effect.
- Figure 7b – Photograph depicts a low magnification view of connective tissue and synthetic mesh. The magnification is too low to comment on Dr. Iakovlev's labeling.
- Figure 7c – Photograph depicts atrophied striated muscle with surrounding fibrous tissue. These findings are entirely consistent with the normal traumatic effect to the pelvic diaphragm of pelvic laxity and pelvic organ prolapse. The absence of synthetic material would support that this effect is completely unrelated to mesh.
- Figures 7d,e,f – The mesh material and surrounding foreign body giant cell reaction in the photograph fail to conform to the definition of "scar plate" as offered by Klinge and colleagues. The presence of normally appearing nerves in this area indicates normal innervation of tissue. The striated muscle with intervening fibrous tissue is consistent with the damage seen with pelvic laxity in pelvic organ prolapse and is unrelated to the mesh.
- Figure 7g – The presence of striated muscle next to mesh is not unexpected when repairing the damaged urogenital diaphragm, as it contains weakened striated muscle fibers.
- Figure set 8a-f – The images show the presence of mesh fibers with the usual foreign body giant cell reaction in their immediate vicinity. Normally appearing

fibrous connective tissue and smooth muscle are present in close proximity. The absence of significant inflammation or fibrosis indicates the biocompatible nature of the mesh. Despite Dr. Iakovlev's statements in number 13 on page 17 of his report, the mere presence of mesh near these tissues does not indicate an adverse effect on the functionality of these tissues. Instead, the mesh likely performs a useful function to return those organs to their normal anatomical position and aids the patient's pre-existing pelvic organ prolapse.

- Figure 9a – The photographs in both panels highlight a blood vessel that has undergone thrombosis, fibrosis, but where recanalization has not occurred. Absence of recanalization is indicative of a complete interruption of that blood vessel. Such an interruption would only occur at the time of the surgery where the mesh was placed.
- Figure 9b (1) – Both panels also depict a thrombosed, not recanalized, fibrotic artery, which would indicate complete transection. An event likely to have occurred at the time of mesh insertion.
- Figure 9b(2) -- Figure 9b purports to show thrombosed capillaries. Each photograph depicts a small capillary containing fibrin but abundant blood in the lumen. The findings are inconclusive evidence of thrombosis.
- Figures 10a-h, 11a-c – See previous discussion on structural changes. In addition, Dr. Iakovlev's colored-in patterns are a speculative explanation for the patterns that the actual fibers are forming in the tissue. One can easily draw in patterns from a third dimension that would also conform to the fibers in that tissue as mesh consists of an intersecting array of fibers. His labeling of scar again misrepresents dense

connective tissue containing normal histologic features such as vessels and nerves in an appropriate distribution and does not represent scar.

- Figures 11a,b,c – Depict connective tissue with mesh, with an area of mixed inflammation consistent with mesh erosion. Erosion is a well-described, rare complication of a midurethral sling.
- Figure12a – Photos depict ulcerated mucosa with acute inflammation and granulation tissue that are consistent with mesh exposure. Erosion is a well-described, rare complication of a midurethral sling.
- Figure 12b – The level of magnification is too low to verify Dr. Iakovlev's findings of bacterial colonies.
- Figures12c,d,e -- Depicts mucosa and underlying connective tissue with mesh, with an area of inflammation consistent with mesh erosion.
- Figure 12f – Reveals connective tissue containing mesh and an area of inflammation without mucosa apparent at this low level of magnification.
- Figure 12g -- Depicts mucosa and underlying connective tissue with mesh, with an area of inflammation consistent with mesh erosion.
- Figure12h – The magnification of this image is too low to assess the type of inflammation or its quantity accurately.
- Figures 20a,b – The presence of dystrophic calcification as seen in these images can be seen in the absence of foreign material. Dystrophic calcifications rarely, if ever, lead to adverse effects on the tissues in which they are encountered.

IV. Response to Non-Pathology Experts' Cancer Claims

Certain of Plaintiffs' experts have claimed that there is a risk of sarcoma or cancer formation with polypropylene. The mice studies and few case reports mostly arising from hernia mesh are methodologically flawed and do not show an association or causation.[76,77] Moreover, they are not transferable to transvaginal mesh and there is no reliable evidence to conclude that there is any association or causal connection with sarcoma formation or malignancy in humans.[78,79,80]

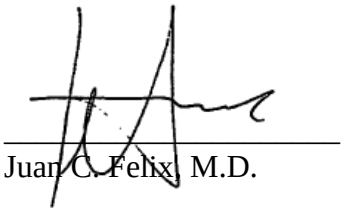
V. Compensation

My hourly rate for activities through expert report is $500. My deposition hourly rate is $600 ($800 for video depositions). My hourly rate for trial testimony is $2,000.

VI. Testimonial History

A list of the cases in which I have testified at deposition or at trial in the last four years is attached as Exhibit C.

Dated: March 2, 2016



Juan C. Felix, M.D.

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